UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,844	11/19/2003	Debra A. Schwinn	1579-869	3968

23117 7590 11/20/2006

NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/715,844	SCHWINN, DEBRA A.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-35* is/are pending in the application.

4a) Of the above claim(s) *8-24,27,28 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,26,29-31 and 33-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed October 2, 2006, 2006. Currently, claims 8-35 are pending. Claims 8-24, 27-28, 32 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election with traverse of Group I, Claims 1-7 in the paper filed January 17, 2006 is acknowledged.

The response asserts that there would be no burden to search the entire application. This argument has been thoroughly reviewed, but not found persuasive because each of the groups are separately classified which provides a prima facie support for burden. For all of the reasons previously presented, the methods and products are distinct.

The requirement is still deemed proper and is therefore made FINAL.

This application contains claims drawn to an invention nonelected with traverse in the paper filed January 17, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Newly submitted claims 27-28, 32 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Each DNA polymorphisms is patentably distinct. A search for G247R is not coextensive

of a search for V311I. Each polymorphism is not obvious over any other polymorphism. The original claims encompassed the single polymorphism of G247R which was treated on the merits. In the event a generic claim becomes allowable, applicant would be entitled to the species encompassed by the claims.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 27-28, 32 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Priority

3. This application claims priority to provisional application 60/427,219, filed November 19, 2002.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 25-26, 29, 31, 33-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The pending claims encompass a large genus of nucleic acids which comprise polymorphisms in any region of any alpha1A adrenergic receptor gene. The claims encompass a large number of polymorphisms and mutations for which no written description is provided in the specification. As provided in Example 11, no common structural attributes identify the members of the genus. The general knowledge and

level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus of alterations in alpha1A adrenergic receptor is highly variant, the specific mutations taught alone is insufficient to describe the genus. There is no description of the mutational sites that exist in nature and there is no description of how the structure of alpha1A adrenergic receptor relates to the structure of any strictly neutral alleles.

The alterations to be detected by methods of the invention are nucleic acid mutations including missense and nonsense mutations as well as deletions, transpositions, insertions, and insertions that alter the structure, function, or expression of the alpha1A adrenergic receptor gene.

The general knowledge in the art concerning variants does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. The common attributes are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim.

The specification provides no correlation between structure of polymorphisms and the function of such polymorphisms with any disease. The polymorphisms shown are not representative of the genus of any polymorphism associated with diseases

because it is not clear which, if any, polymorphisms in alpha1A adrenergic receptor would have the same affect.

Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Response to Arguments

The response traverses the rejection. The response asserts that the claims encompass point mutations that result in an amino acid substitution in a specified region of the alpha1aAR gene. This argument has been considered but is not convincing because the claim remains drawn to any polymorphism which affects the amino acid sequence of the gene. The specification fails to provide a representative number of mutations which change the amino acid and which are associated with disease. Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112-- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Newly added Claims 25-26, 29-31, 33-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 25-26, 29-31, 33-35 are drawn to a method of detecting disease, including cardiovascular disease, cancer or a psychiatric disease, in a patient by screening DNA present in the sample for at least on mutation in alpha1A adrenergic receptor gene.

The nature of the invention, therefore, requires the knowledge of predictive associations between any alteration in any alpha1A adrenergic receptor gene nucleic acid for any subject and diagnosis of any disease.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches the lack of association between mutations in the alpha1A Adrenergic receptor and diseases.

Bolonna et al. (Neruoscience Letters, Vol. 280, pages 65-68, 2000) teaches no influence of adrenergic receptor polymorphisms on schizophrenia and antipsychotic response. Analysis of the Arg492Cys polymorphism in alpha1A Adrenergic receptor did not show a clear difference between the different groups suggesting that the polymorphism did not play an important role in the aetiology of the disorder or in determining antipsychotic response (abstract, Table 1).

Forleo et al. (JACC, page 274A, March 19, 2003) teaches no significant differences were found between alpha1A Adrenergic receptor polymorphisms and non-sustained ventricular tachycardia or altered baroflex sensitivity.

Sofowora et al. (Clin.. Pharmacol. Ther. Vol. 75, pages 539-545, 2004) teaches alpha1A Adrenergic receptor polymorphism and vascular response. The Arg 347Cys polymorphism does not alter agonist-mediated venoconstriction in vivo (abstract). Sofowora states that although our study indicates that the Arg347Cys alpha1A Adrenergic receptor polymorphism is not responsible for differences in phenylephrine responsiveness, other possible polymorphisms may exist, suggesting further experimentation is required (page 543, col. 2). Specifically Sofowora teaches that further study is required to identify other polymorphisms in the alpha1A Adrenergic receptor (page 543, col. 2).

Clark et al. (Biol. Psychiatry, Vol. 58, pages 435-439, 2005) teaches polymorphisms in the promoter region of the alpha1A Adrenergic receptor and association with schizophrenia. Analysis of 8 SNPs was performed and association was found for the –563 SNP and –9625 SNP, however the other 6 polymorphisms did not show an association. Thus, it is unpredictable which polymorphisms are and which polymorphisms are not associated with schizophrenia.

The art teaches genetic variations and associations are often irreproducible.

Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

The art teaches that presence of SNPs in the same gene does not indicate that each of the genes is associated with the same diseases. Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpkl5 and cadpkl6 are not associated with the disease, however cadpkl7 has a p-value of less than 0.05, therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that

the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease.

Guidance in the Specification.

The specification provides no evidence that any mutation or alteration in the alpha1A Adrenergic receptor is associated with a disease, including a cardiovascular diseases, a psychiatric disease or cancer.

The specification teaches SNPS a nucleotides 460, 497, 599, 739, 931, 1039, 1395 of the human alpha1A Adrenergic receptor.

The specification teaches the frequency of each of the polymorphisms in various populations including black, Hispanic and Caucasian groups. The Mutation at 247 is not present in black or Caucasian individuals. Hispanic individuals are the only individuals which appear to exhibit the polymorphism. Thus, detecting disease using the polymorphism in black and Caucasian individuals would be unpredictable.

The specification does not specifically analyze the presence of any of the polymorphisms with any of the diseases.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied

The claims recite "alpha1A Adrenergic receptor gene", however the specification provides no express definition for what makes a sequence a "alpha1A Adrenergic

receptor gene" sequence. alpha1A Adrenergic receptor gene thus appears to encompass variants and homologs, which have not been taught by the instant specification.

The instant specification teaches that the frequency of each of the polymorphisms in various populations including black, Hispanic and Caucasian groups. The Mutation at 247 is not present in black or Caucasian individuals. Hispanic individuals are the only individuals which appear to exhibit the polymorphism. Thus, detecting disease using the polymorphism in black and Caucasian individuals would be unpredictable. Since the polymorphism is not present in black or Caucasian individuals, it would be unpredictable to detect disease in these patients by detecting the polymorphism.

The claims are not limited to human biological samples for detecting alterations. The specification has provide no teachings of any alpha1A Adrenergic receptor gene for any such species. There are no teachings of a gene sequence for any human VCP genes nor what would be the differences between a human mRNA and that of any other mammal.

The specification teaches only 9 specific polymorphisms in relation to the protein amino acid position which is not commensurate in scope with the invention as broadly as it is claimed. The specification fails to teach any correlation of other alterations including deletions, transpositions, insertions or inversions encompassed by the claims and an association with a disease. No common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphisms with any diseases is provided. The specification fails to provide a predictable correlation

with any alteration and a disease. As provided by the art, genetic association studies are unpredictable, even within the same gene which shows association with a disease. The prior art and the post filing date art specifically teach polymorphisms within the alpha1A Adrenergic receptor gene which are not associated with particular diseases. For example, Bolonna teaches an analysis of the Arg492Cys polymorphism in alpha1A Adrenergic receptor did not show a clear difference between the different groups suggesting that the polymorphism did not play an important role in the aetiology of the disorder or in determining antipsychotic response (abstract, Table 1). Therefore, it is clear that it is unpredictable whether particular polymorphisms in the alpha1A Adrenergic receptor gene are associated with a disease, including a psychiatric disease.

The specification provides no evidence that any SNP at such position, in either humans, or mice or dogs for example provides a predictable association with a disease, including psychiatric disease or cancer. The quantity of experimentation in this area is extremely large as it requires analysis of each position in "any" alpha1A Adrenergic receptor gene to determine whether any alteration at each position is associated with a disease, with the outcome of each analysis being unpredictable. While one could conduct additional experimentation to determine whether, e.g. other positions in the alpha1A Adrenergic receptor gene might be associated with a disease in any other patient, the outcome of such research cannot be predicted and such further research and experimentation is both unpredictable and undue. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art teaches the unpredictability of polymorphism association studies, the instant claims are not enabled over the broad scope. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts that none of the references cited by the Examiner relate to point mutations that result in amino acid changes but are rather directed to non-coding sequence or sequence encoding the C-terminus. This argument has been considered but is not convincing because the Claims, namely Claim 32 encompasses the C-terminus, although Claim 31 does not include the C-terminus. The references illustrate the unpredictability of SNPs regardless of their region in the gene. The art provides significant teachings regarding the unpredictability of mutation associations. Furthermore, the response does not appear to address the unpredictability of various animals, and SNPs.

Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

New Matter

6. Claims 25-26, 39, 31, 33-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "an amino acid substitution in a transmembrane helix" or "intracellular loop" are included. The amendment does not point to support in the instant specification for the generic teachings of a transmembrane helix or an intracellular loop. However, the specification does not broadly describe or discuss "an amino acid substitution in a transmembrane helix" or "intracellular loop". Instead the specification particular SNPs in the TM4, TM5 TM7 and IL3. This description does not support "an amino acid substitution in a transmembrane helix" or "intracellular loop". The concept of "an amino acid substitution in a transmembrane helix" or "intracellular loop" does not appear to be part of the originally filed invention. Therefore, "an amino acid substitution in a transmembrane helix" or "intracellular loop" constitutes new matter.

Further, Claim 31 is drawn to a portion of the alpha1aAR gene other than the C-terminus. Similarly, this negative limitation is not supported by the instant specification. Applicant is required to cancel the new matter in the reply to this Office Action.

Conclusion

7. No claims allowable.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
November 13, 2006